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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/846,658	05/01/1997	JOHN ROBERT ADAIR	CARP-0057	9631

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding..

Office Action Summary	Application No.	Applicant(s)	
	08/846,658	ADAIR ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include art not previously cited.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 24-31 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 102(e)/103

Claims 24-31are rejected under 35 U.S.C. 102(e) as anticipated by Queen et al (US 5,585,089), which claims as priority, SN=07/290,975, filed on 12/28/1988, and SN= 08/310,252, filed 02/13/1989, or in the alternative, as being obvious over Queen et al (US 5,585,089).

Claims 24-31 are drawn to:

1) A humanized immunoglobulin comprising amino acids from the donor immunoglobulin framework "outside both" the Kabat CDRs and the structural loop CDRs of the variable regions, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain framework, and each of said donor amino acids contributes to antigen binding as determined by X-ray crystallography, and wherein the humanized immunoglobulin specifically binds to an

antigen with an effective antigen binding affinity (claim 28), or similar to that of the donor immunoglobulin (claim 29), or an affinity constant of at least $10^8\ M^{-1}$ (claim 24), or in the range 10^8-$10^{12}\ M^{-1}$ (claim 26).

2) A humanized antibody of claim 24, wherein the antigen is an IL-2 receptor (claim 26), or wherein the donor immunoglobulin is the anti-CD4 T-cell receptor antibody (claim 27)

3) A humanized antibody of claim 28, wherein the antigen is a human CD3 T-cell receptor (claim 30), or wherein the donor immunoglobulin is the anti-CD3 T-cell receptor antibody (claim 31).

A. Queen et al (US 5,585,089) teach:

A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10.sup.7 M.sup.-1 and no greater than about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the Kabat and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid in the acceptor is rare at its position for human immunoglobulin sequences (claim 4).

In the prior application 07/290,975, filed on 12/28/1988, Queen et al teach that the variable regions of each light/heavy chain pair form the antibody binding site and that the chains all exhibit the same general structure of relatively conserved framework regions joined by three "hypervariable regions", "also called CDR's" (see Kabat et al, 1983 **and** Chothia et al, 1987, which are **incorporated herein by reference** (emphasis added) (Queen et al, 07/290,975, p.8, last paragraph, bridging p.9, lines 1-5).

Queen et al, 07/290,975, teach that the framework regions can vary from the original structure by several amino acid substitutions, terminal and intermediate additions and deletions (Queen et al, 07/290,975, p.12, lines 14-17).

More specifically Queen et al teach the following three criteria:

1) Queen et al teach that more specifically, optional substitutions of a human framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from a donor immunoglobulin will be made at positions in the immunoglobulin where:

The amino acid of the human acceptor framework region is rare (Queen et al, , 07/290,975, p. 21, item 2, lines 23-27, and 08/310,252, filed 02/13/1989, p.4, lines 7-15).

Queen et al further teach that in the specific example of anti-Tac immunoglobulin where the CDR is as defined by Kabat, the replaced rare amino acids in the heavy

chain are amino acids 27, 93, 95, 98, 107-109, 111 (Queen et al, 07/290,975, p. 21, item 2, lines 23-27, and Queen et al, 08/310,252, p.21, item 2, lines 23-26).

It is noted that:

a) the first heavy chain hypervariable loop (CDR1) as taught by Kabat, (which is the same as the first hypervariable loop by sequence) extends from amino acids 31-35, and the heavy chain CDR1 as taught by Chothia (which is the same as the first hypervariable loop by structure) extends from amino acids 26 to 32, and

b) the locations of the hypervariable regions are similar by either sequence or structural criterion, except for the first hypervariable loop of the heavy chain (Winter et al, US 6,548,640B1, column 21, first paragraph).

It is further noted that the instant application discloses that the antigen binding region preferably comprises a composite of the Kabat and structural loop CDR1 (residues 26-35), the Kabat CDR2 (residues 50-65) and Kabat CDR3 (95-100) (p.8, second paragraph).

It is clear that the replaced rare amino acids 93, 107-109, 111 in the framework of the Tac immunoglobulin, as taught by Queen et al, 07/290,975, are outside of both the Kabat CDRs (amino acids 31-35) and the structural loop CDRs (amino acids 26-32).

2) Queen et al also teach that optional substitutions of a human framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from a donor immunoglobulin will be made at positions in the immunoglobulin where:

The framework amino acid is immediately adjacent to one of the CDR's (Queen et al, 07/290,975, p.21, item 3, lines 28-30). Said amino acids may make contacts with the antigen, that contribute to affinity; however said contacts are lost when all the framework amino acids are from human acceptor (Queen et al, 08/310,252, p.10, item 2, lines 20-25, p.12, criterion III, lines 17-28).

In the example of the Tac immunoglobulin, the framework amino acids that are immediately adjacent to one of the CDRs are amino acids 30 and 67 (Queen et al, 07/290,975, p.21, item 3, lines 28-30).

It is clear that the replaced amino acid 67, which is immediately adjacent to one of the CDR's and is in the framework of the Tac immunoglobulin, as taught by Queen et al, 07/290,975, is outside of both the Kabat CDRs (amino acids 31-35) and the structural loop CDRs (amino acids 26-32).

3) Queen et al further teach that optional substitutions of a human framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from a donor immunoglobulin will be made at positions in the immunoglobulin where:

The replaced framework amino acid is physically close to the antigen binding region, as suggested by 3-dimensional modeling (Queen et al, 07/290,975, p.21, item 4, lines 31-34, Queen et al, 08/310,252, p.10, item 1, lines 11-19, p.12, criterion IV, lines 30-37, bridging p.13). These acceptor framework human amino acids that are close to the CDR's can slightly distort the CDR's, because they create different electrostatic or hydrophobic forces (hydrogen bonding, Van-der Waals forces, hydrophobic interactions etc..) than in the donor mouse antibody, and the distorted

CDR's may not make as effective contacts with the antigen as the CDR's in the donor antibody (Queen et al, 08/310,252, p.10, item 1, lines 11-19, p.12, criterion IV, lines 30-37, bridging p.13).

In the specific example of anti-Tac immunoglobulin, where the CDR is as defined by Kabat, Queen et al teach that the replaced amino acids in the heavy chain that are close to the CDR's are amino acids 48 and 68 (Queen et al, 07/290,975, p.21, item 4, lines 31-34)

It is clear that the replaced amino acids 48, 68, which are physically close to the antigen binding region, as suggested by 3-dimensional modeling and are in the framework of the Tac immunoglobulin, as taught by Queen et al, 07/290,975, are outside of both the Kabat CDRs (amino acids 31-35) and the structural loop CDRs (amino acids 26-32).

Further, the hypervariable regions, also called CDRs, as described by Kabat and Chothia are known in the art, and are incorporated by reference by Queen et al (Queen et al, 07/290,975, p.8, last paragraph, bridging p.9, lines 1-5).

In summary, **many of the replaced amino acids in the framework of a humanized immunoglobulin, as taught by Queen et al, that belong to at least one of the following three categories: (I) adjacent to a CDR in the donor immunoglobulin sequence, or (II) capable of interacting with amino acids in the CDRs, or (III) rare at its position for human immunoglobulin sequences (three categories in Queen et al, 08/310252, p. 10-13, and claim 4 of Queen et al, US 5,585,089), are "inherently" outside of both the CDRs as described by Kabat,**

"and" the structural loop CDRs as described by Chothia et al, wherein CDRs as described by Kabat and Chothia are known in the art, as incorporated in reference by Queen et al.

In other words, the limitation of "a humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the Kabat and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid in the acceptor is rare at its position for human immunoglobulin sequences" as taught in claim 4 in Queen et al, US 5,585,089, clearly has support in the prior applications of Queen et al, 07/290,975 and 08/310252.

B. In addition, Queen et al teach, as an example, humanizing an immunoglobulin specific for IL-2 receptor (anti-Tac), which has a binding affinity of at least about $10^8\ M^{-1}$, and preferably $10^9\ M^{-1}$ to $10^{10}\ M^{-1}$ or stronger (Queen et al, 07/290,975, item under Summary, on page 4, and p.8 first paragraph). Queen et al also teach that the anti-Tac and the humanized anti-Tac have approximately the same affinity (Queen et al, 07/290,975, p.26, last paragraph, bridging p.27).

The binding affinity of the humanized immunoglobulin taught by Queen et al is clearly within the range of the claimed binding affinity. The humanized immunoglobulin

taught by Queen et al also has a binding affinity similar to that of the donor immunoglobulin.

Queen et al further teach that the humanizing method can be used in combination with monoclonal antibodies reactive with (Queen et al, 07/290,975, page 15, last paragraph, bridging p.16), or can be used to humanize antibodies reactive with (Queen et al, 08/310,252, page 18, last paragraph, bridging page 19) other markers on cells responsible for diseases, such as T cell markers in the group of "clusters of differentiation", as named by the first International Leukocyte differentiation workshop, Leukocyte typing, 1984, **which is incorporated herein by reference**.

The humanized immunoglobulin taught by Queen et al (07/290,975 and 08/310,252) clearly encompasses immunoglobulin that binds to antigen IL-2 receptor (see for example Queen et al, 07/290,975, item under Summary, on page 4, and p.8 first paragraph), or immunoglobulin that binds to antigen, which is CD-4 T-cell receptor or CD3 T- cell receptor, because Lohmeyer J et al, 1987, Blut, 54(4): 223-9, teach that using a large panel of monoclonal antibodies corresponding to the clusters of differentiation antigens established on the Leukocyte typing Workshop I and II reveals unique T-cell phenotype, which includes CD3 and CD4.

Thus all the limitations of the claims of the instant application are met by the teaching of Queen et al, US 5,585,089, which is supported in the teaching of Queen et al, 07/290,975 and 08/310,252.

ANSWERS TO APPLICANT'S ARGUMENTS AGAINST 102(e) REJECTION

A. Applicant argues that the Queen patent, US 5,585,089 contains limitations that are not found in the earliest priority documents:

1. Affinity constant of at least 10^7M^{-1},

2. No greater than about four-fold that of the donor immunoglobulin, and

3. Outside the Kabat and Chothia CDRs".

It is noted that the limitations items 1 and 2 are not germane to the instant claims, because said limitations are not found in the instant claims.

Therefore, only arguments related to the limitation "outside of the Kabat and Chothia CDRs" are addressed here (see below).

B. Applicant discusses the prosecution of one of Queen's application, 07/634278, now patented, US 5,530,101, with Queen's arguments against Riechman reference, which is cited to support an obviousness rejection.

The recitation of Queen's arguments in 07/634278, now patented, US 5,530,101, is not germane, because each case is decided on its own facts. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

C. Applicant argues that the two earliest priority applications did not require that there be changes to donor in the framework outside both the Kabat **and** Chothia CDRs.

Applicant argues that rather they describe a single change to donor anywhere in the framework, including residues within the first Chothia heavy chain CDR (residues

26-32), or even, no change to donor in the framework.

Applicant argues that the passage relied upon by the Office, i.e. on page 9, lines 1-5 of the 975 application contains the background discussion of the hypervariable regions, which it reports are also called CDRs, and incorporates by reference Kabat and Chothia. Applicant argues that this passage is the only one in the 975 application linking Chothia to the term CDRs. Other passages specifically referring to CDRs make it clear that the CDRs are as defined by Kabat. Applicant argues that, for example, residue 27 and 30 to be changed to donor, both of which are within the first heavy chain Chothia CDR, and that residue 30, listed as a position immediately adjacent to a CDR, is adjacent only to the first Kabat heavy chain CDR, but within the first Chothia heavy chain CDR.

Applicant argues that similarly, the passage relied upon by the Office, i.e. on page 13, lines 1-18 of the 252 application is in the context of computer programs, and there is no reference to CDRs.

Applicant argues that the specification of Queen et al does not define the term CDRs as meaning Kabat and Chothia, but rather the specification defines CDRs in terms of Kabat, as shown in the general protocol set forth at column 14 of Queen patent (Category 1: The amino acid position is in a CDR is defined by Kabat).

Applicant's arguments set forth in paper of 02/14/05 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, the teaching in Queen et al, US 5,585,089, clearly has support in the prior applications of Queen et al, 07/290,975 and 08/310252.

It is clear that m**any of the replaced amino acids in the framework of a humanized immunoglobulin, as taught by Queen et al, that belong to at least one of the following three categories: (I) adjacent to a CDR in the donor immunoglobulin sequence, or (II) capable of interacting with amino acids in the CDRs, or (III) rare at its position for human immunoglobulin sequences (three categories in Queen et al, 08/310252, p. 10-13, and claim 4 of Queen et al, US 5,585,089), are "inherently" outside of both the CDRs as described by Kabat, "and" the structural loop CDRs as described by Chothia et al, wherein CDRs as described by Kabat and Chothia are known in the art, as incorporated in reference by Queen et al, *supra*.**

In other words, the limitation of "a humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the Kabat and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid in the acceptor is rare at its position for human immunoglobulin sequences" as taught in claim 4 in Queen et al, US 5,585,089, clearly has support in the prior applications of Queen et al, 07/290,975 and 08/310, 252.

Further, it is noted that there is no limitation in Queen et al that the CDRs has to be specifically Kabat CDRs when humanizing immunoglobulin. For example, in a

general protocol teaching humanizing immunoglobulin by replacing the framework amino acid(s) that belongs to at least one of the following three categories: (I) adjacent to a CDR in the donor immunoglobulin sequence, or (II) capable of interacting with amino acids in the CDRs, or (III) rare at its position for human immunoglobulin sequences, only the generic term framework is referred to (Queen et al, 08/310,252, pages 10-13). It is further noted that mainly in specific examples using Tac immunoglobulin that the CDRs are defined as Kabat CDRs (for example, Queen et al, 07/290,975, item under Experimental, pages 21-22, Queen et al, 08/310,252, item under Experimental, pages 21-22). Thus the teaching of Queen et al does not limit that the framework has to be Kabat framework, in view of the above, and in view of the incorporation by reference, by Queen et al, 07/290,975, of Kabat and Chothia concerning hypervariable region or CDRs.

D. On page 18, Applicant again discusses the prosecution of another Queen's application, reciting Queen's arguments against the Riechman reference.

On pages 18-20, Applicant discusses the prosecution of Queen's European patent 451,216, reciting Queen's arguments.

The recitation of Queen's arguments in other Queen's applications is not germane, because each case is decided on its own facts. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

E. On pages 21-23, Applicant argues that the Office changes position, when argues

that the Office means that CDRs as taught by Queen et al, could be interpreted as either Kabat **or** Chothia CDRs, rather than Kabat **and** Chothia CDRs.

Applicant argues that regardless, the record of the Queen patent does not support this latter interpretation of CDRs either, i.e. either Kabat or Chothia CDRs. Applicant argues that the first limitation of claim 1 of Queen patent US 5,585,089 does not recite Kabat or Chothia CDRs but merely CDRs. Applicant argues that the specification does not define the term "CDRs" as meaning Kabat or Chothia. Applicant argues that interpretation of CDRs of claim 1, as either Kabat or Chothia would make the recitation "outside the Kabat and Chothia CDRs" of claim 1 superfluous.

This is not found to be persuasive.

The Examiner did not change the position. The Examiner apologizes that the passage in the Office action of March 2003, page 4, is confusing to Applicant. As asserted in the Office action of August 2003, sentence bridging pages 3-4, the Examiner means that the CDRs, **as incorporated by reference** by Queen et al in the 07/290975 application, could be interpreted as either Kabat or Chothia CDRs.

It is noted the language "wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the Kabat and Chothia CDRs" in claim 1 of Queen patent US 5,585,089 imposes the limitation that the replaced amino acids of the framework comprises amino acids that are outside of the Kabat and Chothia CDRs. There is no limitation as how one would interpret the first mentioned language "CDRs" of claim 1 of Queen patent US 5,585,089.

Said limitation that the replaced amino acids of the framework comprises amino acids that are outside of the Kabat and Chothia CDRs is certainly supported by the prior applications of 07/290,975 and 08/310,252 of Queen et al, supra.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

April 26, 2005

SUSAN UNGAR, PH.D
PRIMARY EXAMINER